FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) Meeting
FDA White Oak Campus, Building 31, The Great Room (Rm. 1503)
White Oak Conference Center, Silver Spring, Maryland
May 24, 2012

Questions to the Committee

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1. **DISCUSSION**: Please discuss the strengths and weaknesses of study 005, including the effects of the following factors on its ability to provide substantial evidence of effectiveness. Please discuss how regulatory flexibility might be applied with regard to these factors.

    a. p-value for the pre-specified co-primary endpoint

    b. Nominal p-values for the individual components of the co-primary endpoint

    c. p-value for efficacy-evaluable population

    d. Lack of control for multiple testing in the analyses of secondary endpoints

    e. Results of secondary endpoints

    f. Baseline imbalances

    g. Disproportionate support of efficacy from site 1 in Portugal, with little to no efficacy support from combination of remaining sites

2. For approval based on a single study plus confirmatory evidence, the study is expected to be particularly robust. Note, however, that not all characteristics that might make a study particularly robust need to be present.

    a. **VOTE**: In the context of the above discussion, are the findings of study 005 sufficiently robust to provide substantial evidence of efficacy similar to that usually provided by two supportive studies for a ***clinical*** endpoint?

        i. If you voted "Yes" in question #2a, please discuss how.

    b. **VOTE**: In the context of the above discussion, are the findings of study 005 sufficiently robust to provide substantial evidence of efficacy similar to that usually provided by two supportive studies for a ***biomarker*** endpoint that is reasonably likely to predict a clinical benefit?

        i. If you voted "Yes" in question #2b, please discuss how.

3. **VOTE**: If the answer to Question #2a and #2b is "No", is study 005 'positive' in the sense of providing evidence of similar robustness to that provided by a single study with primary endpoint with a p-value less than or equal to 0.05?

Questions to the Committee (cont.)

4. **DISCUSSION**: Study 006 does not have the characteristics of an adequate and well-controlled trial, but may provide supportive evidence of effectiveness for tafamidis. Please discuss the strengths and weakness of study 006 as a source of supportive evidence, including the effect of the following factors:

    a. Analysis of many endpoints without control for multiple testing

    b. Dependence on differences between arms present at the end of study 005

    c. Imbalances present in study 005

    d. Open-label design (including, for example, risk of unblinding and bias from non-random dropouts)

5. **VOTE**: Does study 006 provide supportive evidence of efficacy?

    a. If you voted "Yes" in question #5, please discuss how.

6. **DISCUSSION**: Please discuss if there is other evidence that is particularly persuasive of efficacy. If so, what?

7. **DISCUSSION**: Please discuss if there are any particular concerns about safety.